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(54) Title: SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEMS

(57) Abstract: The present invention relates to self-microemulsifying drug delivery systems ("SMEDDS") of selective partial adenosine A1 receptor agonists, with enhanced bioavailability, and a process of preparing said SMEDDS.



Self-microemulsifying drug delivery systems

The present invention relates to self-microemulsifying drug delivery systems ("SMEDDS") of selective partial adenosine A1 receptor agonists, with enhanced bioavailability, and a process of preparing said SMEDDS.

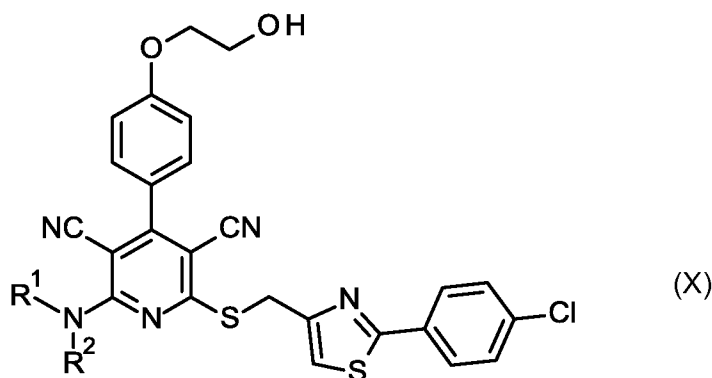
- 5 Poor soluble drugs in their crystalline form often show poor bioavailability. This might be managed by transforming the crystalline into a dissolved / solubilized form, e.g. by using SMEDDS.

Self-microemulsifying drug delivery systems ("SMEDDS") are known as formulations useful for the oral administration of drugs (see *Eur. J. Pharm Sci.* **2000**, 11 Suppl. 2, S93-S98). A SMEDDS is a mixture of a drug, an oil or lipid, a surfactant, and optionally a co-solvent or co-surfactant, that
 10 rapidly forms a transparent (or at least translucent), stable microemulsion upon dilution with water (see *Eur. J. Pharm Sci.* **2009**, 38, 479-488). SMEDDS offer numerous advantages: spontaneous formation, ease of manufacture, thermodynamic stability, and improved solubilization of bioactive materials (see *Adv. Colloid Interface Sci.* **2006**, 128-130, 47-64).

The invention thus provides a composition comprising

- 15 (a) a selective partial adenosine A1 receptor agonist,
 (b) an oil or lipid,
 (c) a surfactant, and
 (d) optionally a co-solvent or co-surfactant, or both.

Selective partial adenosine A1 receptor agonists according to this invention are compounds of the
 20 formula (X)



in which

R¹ represents (C₁-C₄)-alkyl,

R² represents (C₁-C₄)-alkyl,

- 25 where (C₁-C₄)-alkyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of fluorine, trifluoromethyl, trifluoromethoxy, (C₁-C₄)-alkoxy, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkoxy and (C₁-C₄)-alkylsulphonyl,

or

R¹ and R² each represent hydrogen

or

R¹ and R² together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycle which may contain a further heteroatom from the group consisting of N, O and S,

where the 4- to 7-membered heterocycle may be substituted by 1 to 2 substituents independently of one another selected from the group consisting of fluorine, trifluoromethyl, (C₁-C₄)-alkyl, trifluoromethyl and (C₁-C₄)-alkoxy,

and the salts, solvates, and solvates of the salts thereof.

Depending on their structure, the compounds according to the invention may exist in stereoisomeric forms (enantiomers, diastereomers). The invention therefore encompasses the enantiomers or diastereomers and the respective mixtures thereof. It is possible to isolate the stereoisomerically homogeneous constituents from such mixtures of enantiomers and/or diastereomers in a known manner.

If the compounds according to the invention can occur in tautomeric forms, the present invention encompasses all the tautomeric forms.

Preferred salts in the context of the present invention are physiologically acceptable salts of the compounds according to the invention. Also encompassed are salts which are not themselves suitable for pharmaceutical applications but can be used, for example, for isolation or purification of the compounds of the invention.

Physiologically acceptable salts of the compounds according to the invention include acid addition salts of mineral acids, carboxylic acids and sulphonic acids, for example salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, trifluoroacetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Physiologically acceptable salts of the compounds of the invention also include salts of conventional bases, by way of example and with preference alkali metal salts (e.g. sodium and potassium salts), alkaline earth metal salts (e.g. calcium and magnesium salts) and ammonium salts derived from ammonia or organic amines having 1 to 16 carbon atoms, by way of example and with preference ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methylmorpholine, arginine, lysine, ethylenediamine and N-methylpiperidine.

Designated as solvates in the context of the invention are those forms of the compounds according to the invention which form a complex in the solid or liquid state by coordination with solvent molecules. Hydrates are a specific form of the solvates in which the coordination is with water.

Solvates preferred in the context of the present invention are hydrates.

In the context of the present invention, unless specified otherwise, the substituents are defined as follows:

Alkyl in the context of the invention is a linear or branched alkyl radical having 1 to 4 carbon atoms. Preferred examples include: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

Cycloalkyl in the context of the invention is a monocyclic saturated carbocycle having 3 to 7 ring carbon atoms. Preferred examples include: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Alkoxy in the context of the invention is a straight-chain or branched alkoxy radical having 1 to 4 carbon atoms. Preferred examples include: methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and tert-butoxy.

Cycloalkoxy in the context of the invention is a monocyclic saturated carbocycle which has 3 to 7 carbon atoms and is bonded via an oxygen atom. Preferred examples include: cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy.

Alkylsulphonyl in the context of the invention is a straight-chain or branched alkyl radical which has 1 to 4 carbon atoms and is attached via a sulphonyl group. Preferred examples include: methylsulphonyl, ethylsulphonyl, n-propylsulphonyl, isopropylsulphonyl, n-butylsulphonyl and tert-butylsulphonyl.

Heterocycle in the context of the invention is a saturated heterocycle which has a total of 4 to 7 ring atoms, contains one or two ring heteroatoms from the group consisting of N, O and S and is attached via a ring carbon atom or optionally a ring nitrogen atom. Examples include: azetidiny, pyrrolidiny, pyrazolidiny, tetrahydrofurany, piperidiny, piperaziny, tetrahydropyrany, morpholinyl, thiomorpholinyl and azepanyl. Preference is given to azetidiny, pyrrolidiny, piperidiny and morpholinyl.

In one embodiment of the invention the selective partial adenosine A1 receptor agonists are compounds of the formula (X), in which

R¹ represents (C₁-C₃)-alkyl,

R² represents (C₁-C₃)-alkyl,

where (C₁-C₃)-alkyl may be substituted by 1 or 2 substituents independently of one another selected from the group consisting of fluorine, trifluoromethyl, methoxy, ethoxy, cyclopropyl and cyclobutyl,

or

R¹ and R² each represent hydrogen

or

R¹ and R² together with the nitrogen atom to which they are attached form a 4- to 6-membered heterocycle which may contain a further heteroatom from the group consisting of N, O and S,

where the 4- to 6-membered heterocycle may be substituted by 1 or 2 substituents independently of one another selected from the group consisting of fluorine, trifluoromethoxyl, (C₁-C₄)-alkyl, trifluoromethoxy, methoxy and ethoxy, and the salts, solvates, and solvates of the salts thereof.

- 5 In one embodiment of the invention the selective partial adenosine A1 receptor agonists are compounds of the formula (X), in which

R¹ represents ethyl,

R² represents ethyl,

or

- 10 R¹ and R² each represent hydrogen

or

R¹ and R² together with the nitrogen atom to which they are attached form an azetidiny, pyrrolidinyl or piperidinyl ring,

where the azetidiny ring may be substituted by a methoxy substituent,

- 15 and the salts, solvates, and solvates of the salts thereof.

In one embodiment of the invention the selective partial adenosine A1 receptor agonists are selected from the group consisting of

2-amino-6-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulphanyl)-4-[4-(2-hydroxyethoxy)phenyl]-pyridine-3,5-dicarbonitrile (known from WO 03/053441),

- 20 2-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulphanyl)-6-(diethylamino)-4-[4-(2-hydroxyethoxy)phenyl]pyridine-3,5-dicarbonitrile (known from WO 2010/086101),

2-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulphanyl)-4-[4-(2-hydroxyethoxy)phenyl]-6-(3-methoxyazetidin-1-yl)pyridine-3,5-dicarbonitrile (known from WO 2010/086101),

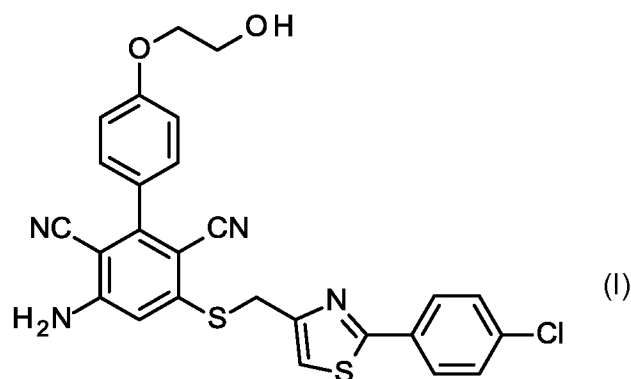
- 25 2-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulphanyl)-4-[4-(2-hydroxyethoxy)phenyl]-6-(pyrrolidin-1-yl)pyridine-3,5-dicarbonitrile (known from WO 2010/086101),

2-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulphanyl)-4-[4-(2-hydroxyethoxy)phenyl]-6-(piperidin-1-yl)pyridine-3,5-dicarbonitrile (known from WO 2010/086101),

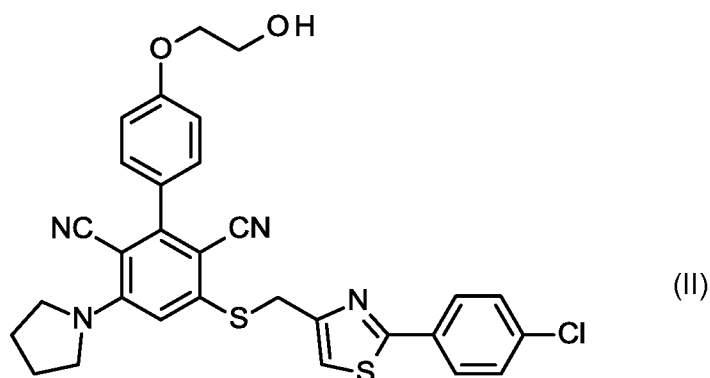
and the salts, solvates, and solvates of the salts thereof.

Selective partial adenosine A1 receptor agonists which may be converted into the compositions according to the present invention are in particular selected from the following list:

- 30 2-Amino-6-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-4-[4-(2-hydroxyethoxy)phenyl]-pyridine-3,5-dicarbonitrile (known from WO 03/053441 and also known as Capadenoson)



2-({[2-(4-Chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-4-[4-(2-hydroxyethoxy)phenyl]-6-(pyrrolidin-1-yl)pyridine-3,5-dicarbonitrile (known from WO 2010/086101 and also known as Neladenoson)



- 5 The selective partial adenosine A1 receptor agonists are present in the compositions according to the invention in a concentration range of 1 to 5 mg/mL, preferably in the range of 1.5 to 3.5 mg/mL, further preferred in the range of 2.25 to 3 mg/mL.

The compounds according to formula (X), in particular according to formula (I) and (II), act as partial adenosine A1 receptor agonists and may be used for the prevention and/or treatment of cardiovascular disorders like e.g. coronary heart disease, ischemic injury during acute coronary syndrome, angina pectoris, heart failure, worsening chronic heart failure, heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), myocardial infarction and atrial fibrillation

Suitable oils or lipids are medium- or long-chain glycerides, which contain fatty acids of varying chain lengths and degrees of unsaturation. Examples of lipid ingredients include synthetic lipids and lipids of natural sources:

Caprol 3GO (i.e. C8:C10 triglyceride), Labrafac® Lipophile WL 1349 {medium chain triglycerides [caprylic (C8) 50-80%, capric (C10) 20-50%]}, Labrafac® PG (propylene glycol dicaprylocarate), Labrafil® M 1944 CS {oleoyl polyoxyl-6 glycerides [oleic (C18:1) 58-68%, linoleic (C18:2) 22-32%]}, Labrafil® M 2125 CS {linoleoyl polyoxyl-6 glycerides [oleic (C18:1) 24-34%, linoleic (C18:2) 53-63%]}, Labrafil® M 2130 CS (lauroyl polyoxyl-6 glycerides), Labrafac® CM 10 {C8-C10 polygly-

colized glycerides [caprylic (C8) 50%, capric (C10) 50%], Labrafil® WL 2609 BS {linoleoyl macrogol glycerides [oleic (C18:1) 24-34%, linoleic (C18:2) 53-63%], Lauroglycol™ 90 {propylene glycol monolaurate Type II [monoesters > 90%, C12 (lauric acid) > 95%]}, Lauroglycol™ FCC {propylene glycol laurate Type I [monoesters 45-70%, 30-55% diester >95% C12], Maisine™ 35-1 {glyceryl monolinoleate [C18:2 >50% max; C18:1 10-35%; C18:0 <6%; C16 4-20%]}, Capryol™ 90 {propylene glycol monocaprylate [>90% monoester of C8 (caprylic acid)]}, Capryol™ PGM C 90 (propylene glycol monocaprylate; >60% Monoester >90% C8), Peceol™ {glyceryl mono-oleate [C18:1 > 60%; C18:2 < 35%; C18:0 < 6%; C16 < 12% 0-5%]}, Plurol oleique® CC497 (polyglyceryl-3 dioleate), Plurol® (diisostearate triglycerol diisostearate), Transcutol® HP [diethylene glycol monoethyl ether (>99.9%)], Transcutol® P (diethylene glycol monoethyl ether), Captex® 355 (caprylic/capric triglyceride), Captex® 200 (propylene glycol dicaprylate/dicaprate), Migliol® 810 {medium chain fatty acids [C8 (65-80%); C10 (20-35%)]}, Migliol® 812 {medium chain fatty acids [C8 (50-65%); C10 (30-45%)]}, Migliol® 840 (medium chain diesters of propylene glycols), Miglyol® 818 {medium chain fatty acids [C8 (45-65%); C10 (30-45%); C18:2 (2-5%)]}, Capmul® MCM {glyceryl monocaprylate [(58% monoglyceride, 36% diglyceride, 5% triglyceride; 80% C8, 20% C10)]}, Capmul® MCM C8 {glyceryl monocaprylate [(68% monoglyceride, 27% diglyceride, 3% triglyceride; >95% C8, 3% C10)]}, Capmul® MCM C10 {glyceryl monocaprylate [(>45% monoglyceride; >45% C10)]}, Imwitor® 742 [monoglyceride/diglyceride/triglyceride of C8 and C10 fatty acid (45-55% monoglyceride)], Imwitor® 928 [monoglyceride/diglyceride/triglyceride of saturated fatty acids of coconut oil (40% MG)], Myrj® 45 {PEG 400 monostearate polyoxy 8 stearate [Stearic (C18) acid]};

or natural product oils from apricot kernel, canola, castor, coconut, corn, olive, palm, palm kernel, peanut, safflower, sesame, soybean, sunflower.

The fatty acid composition of the natural product oils is as follows (see *Drug Dev. Ind. Pharm.* **2013**, 39, 1-19):

Oil	C8	C10	C12	C14	C16	C18	C18:1	C18:1-OH	C18:2	C18:3
Apricot kernel	—	—	—	—	—	1.0	64.2	—	28.3	0.2
Canola	—	—	—	—	4.7	2.0	60.0	—	21.7	9.1
Castor	—	—	—	—	2.0	1.0	7.0	87	3.0	—
Coconut	2.4	2.7	44.4	16.6	9.6	2.8	17.8	—	3.1	0
Corn	—	—	—	—	10.7	1.6	24.5	—	10.7	1.1
Olive	—	—	—	—	12.9	71.2	71.2	—	10.0	0.9
Palm	—	—	—	1.0	45.0	40.0	40.0	—	2.0	—
Palm kernel	—	4.0	48.0	16.0	8.0	15.0	15.0	—	36.0	—
Peanut	—	—	—	—	12.0	48.0	48.0	—	36.0	0
Safflower	—	—	—	—	5.5	11.1	11.1	—	81.4	0.4
Sesame	—	—	—	—	9.0	41.0	41.0	—	45.0	—
Soybean	—	—	—	—	10.4	21.5	21.5	—	51.5	7.8
Sunflower	—	—	—	—	6.2	20.7	20.7	—	67.9	0.2

The lipid is preferably selected from Labrafil® M 1944 CS, Maisine™ 35-1, Capmul® MCM and soybean oil.

To form efficient SMEDDS the selected surfactant should have a hydrophilic-lipophilic balance (HLB) value of 12 or higher, preferably in the range of 12 to 15. Suitable surfactant may thus be selected from:

Labrasol® {caprylocaproyl macrogol-8-glycerides [caprylic (C8) 50-80%, capric (C10) 20-50%]}, Cremophor® EL or ELP (polyoxy-35-castor oil), Cremophor® RH40 (polyoxy-40-hydrogenated castor oil), Cremophor® A25 {Macrogol 25 cetostearyl ether [stearic (C18) and cetyl (C16)]}, Vitamin E® TPGS (Vit E d- α -tocopheryl polyethylene glycol 1000 succinate), Gelucire® 44/14 {lauryl polyoxylglycerides [C12 (40-50%); C14 (14-24%); C8 (4-10%), C10 (3-9%), C16 (4-14%), C18 (5-5%)]}, Gelucire® 50/13 {stearoyl polyoxyl-32 glycerides [C16 (40-50%); C18 (48-58%); C16+18 > 90%]}, Acconon® CC-6 (PEG-6 caprylic/capric glycerides), Brij® 97 {polyoxyl 10 oleyl ether Oleth 10 PEG monooleyl ether [Oleyl (C18:1)]}, or Tween® 80 (polysorbate 80).

Preferred surfactants are Labrasol®, Cremophor® RH40, Cremophor® EL, Cremophor® ELP and Tween® 80.

Co-solvents or co-surfactant are selected from medium chain length alcohols (C2-C8), propylene glycol, PEG 300 or PEG 400.

In addition to the selective partial adenosine A1 receptor agonists the composition according to the invention comprises the following:

The composition according to the invention comprises 10 to 50 % (v/v) of the oil or lipid, more preferably 10 to 30%.

The composition according to the invention comprises 35 to 85 % (v/v) of the surfactant.

The composition according to the invention comprises 0 to 40 % (v/v) of the co-solvent or co-surfactant, preferably 10 to 40%.

Contents of the excipients is given in % (v/v) based on the content of lipid, surfactant and co-solvent or co-surfactant.

Particularly preferred compositions according to the invention comprise the following lipid/surfactant/co-solvent or co-surfactant:

(A) Labrafil® M 1944 CS, Labrasol;

(B) Maisine™ 35-1 or Maisine CC, propylene glycol, Cremophor® RH40 and ethanol;

(C) Capmul® MCM, Cremophor® ELP;

(D) soybean oil, Tween® 80.

In particular preferred are compositions according to the invention comprising one of the following lipid/surfactant/co-solvent or co-surfactant combinations:

(E) 30% Labrafil® M 1944 CS, 70% Labrasol;

(F) 36% Maisine™ 35-1 or Maisine CC, 10% propylene glycol, 40% Cremophore® RH40 and
5 14% ethanol;

(G) 25% Capmul® MCM, 75% Cremophor® ELP;

(H) 16.7% soybean oil, 83.3% Tween® 80.

Further preferred are compositions (A) to (D) containing as active ingredient the compound of formula (I).

10 Further preferred are compositions (A) to (D) containing as active ingredient the compound of formula (II).

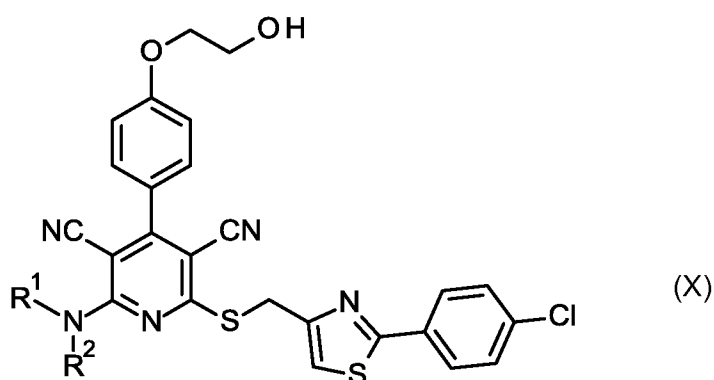
Very particularly preferred are compositions (E) to (H) containing as active ingredient the compound of formula (I).

Very particularly preferred are compositions (E) to (H) containing as active ingredient the compound of formula (II).
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Very particularly preferred is the composition containing as active ingredient the compound of formula (II), 30% Labrafil® M 1944 CS, 70% Labrasol (where the percentages given relate to the content of lipid and surfactant only).

The invention thus provides a composition comprising

20 (a) a partial adenosine A1 receptor agonist of the formula (X)



in which

R¹ represents (C₁-C₄)-alkyl,

R² represents (C₁-C₄)-alkyl,

25 where (C₁-C₄)-alkyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of fluorine, trifluoromethyl, trifluoromethoxy, (C₁-C₄)-alkoxy, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkoxy and (C₁-C₄)-alkylsulphonyl,

or

R¹ and R² each represent hydrogen

or

R¹ and R² together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycle which may contain a further heteroatom from the group consisting of N, O and S,

where the 4- to 7-membered heterocycle may be substituted by 1 to 2 substituents independently of one another selected from the group consisting of fluorine, trifluoromethyl, (C₁-C₄)-alkyl, trifluoromethyl and (C₁-C₄)-alkoxy,

and the salts, solvates, and solvates of the salts thereof,

- (b) an oil or lipid selected from Caprol 3GO (i.e. C8:C10 triglyceride), Labrafac® Lipophile WL 1349 {medium chain triglycerides [caprylic (C8) 50-80%, capric (C10) 20-50%]}, Labrafac® PG (propylene glycol dicaprylocarate), Labrafil® M 1944 CS {oleoyl polyoxyl-6 glycerides [oleic (C18:1) 58-68%, linoleic (C18:2) 22-32%]}, Labrafil® M 2125 CS {linoleoyl polyoxyl-6 glycerides [oleic (C18:1) 24-34%, linoleic (C18:2) 53-63%]}, Labrafil® M 2130 CS (lauroyl polyoxyl-6 glycerides), Labrafac® CM 10 {C8-C10 polyglycolized glycerides [caprylic (C8) 50%, capric (C10) 50%]}, Labrafil® WL 2609 BS {linoleoyl macrogol glycerides [oleic (C18:1) 24-34%, linoleic (C18:2) 53-63%]}, Lauroglycol™ 90 {propylene glycol monolaurate Type II [monoesters > 90%, C12 (lauric acid) > 95%]}, Lauroglycol™ FCC {propylene glycol laurate Type I [monoesters 45-70%, 30-55% diester >95% C12]}, Maisine™ 35-1 {glyceryl monolinoleate [C18:2 >50% max; C18:1 10-35%; C18:0 <6%; C16 4-20%]}, Capryol™ 90 {propylene glycol monocaprylate [>90% monoester of C8 (caprylic acid)]}, Capryol™ PGMC 90 (propylene glycol monocaprylate; >60% Monoester >90% C8), Peceol™ {glyceryl monooleate [C18:1 > 60%; C18:2 < 35%; C18:0 < 6%; C16 < 12% 0-5%]}, Plurol oleique® CC497 (polyglyceryl-3 dioleate), Plurol® (diisostearate triglycerol diisostearate), Transcutol® HP [diethylene glycol monoethyl ether (>99.9%)], Transcutol® P (diethylene glycol monoethyl ether), Captex® 355 (caprylic/capric triglyceride), Captex® 200 (propylene glycol dicaprylate/dicaprate), Migliol® 810 {medium chain fatty acids [C8 (65-80%); C10 (20-35%)]}, Migliol® 812 {medium chain fatty acids [C8 (50-65%); C10 (30-45%)]}, Migliol® 840 (medium chain diesters of propylene glycols), Miglyol® 818 {medium chain fatty acids [C8 (45-65%); C10 (30-45%); C18:2 (2-5%)]}, Capmul® MCM {glyceryl monocaprylate [(58% monoglyceride, 36% diglyceride, 5% triglyceride; 80% C8, 20% C10)]}, Capmul® MCM C8 {glyceryl monocaprylate [(68% monoglyceride, 27% diglyceride, 3% triglyceride; >95% C8, 3% C10)]}, Capmul® MCM C10 {glyceryl monocaprylate [(>45% monoglyceride; >45% C10)]}, Imwitor® 742 [monoglyceride/diglyceride/triglyceride of C8 and C10 fatty acid (45-55% monoglyceride)], Imwitor® 928 [monoglyceride/diglyceride/triglyceride of saturated fatty acids of coconut oil (40% MG)], Myrj® 45 {PEG 400 monostearate polyoxy 8 stearate

[Stearic (C18) acid]]; or selected from natural product oils from apricot kernel, canola, castor, coconut, corn, olive, palm, palm kernel, peanut, safflower, sesame, soybean, sunflower,

(c) a surfactant having a hydrophilic-lipophilic balance (HLB) value of 12 or higher, and

(d) optionally a co-solvent or co-surfactant selected from medium chain length alcohols (C2-C8), propylene glycol, PEG 300 or PEG 400, or both.

Another subject of the invention is a method for preparing the compositions according to the invention. Thereby, the excipients are mixed until a clear solution is obtained. In the second step the active ingredient is dissolved in the excipients mixture under stirring. If necessary, slight warming and sonication by ultrasound is applied to facilitate the dissolution of the active ingredient. The composition according to the invention can be packaged in any pharmaceutical composition for oral administration.

Suitable oral compositions that comprise the composition according to the invention are generally capsules, including hard gelatin capsules or soft gelatin capsules. For instance, soft gelatin capsules are made with a gelatin shell, optionally in association with plasticizers such as glycerine and/or sorbitol. Encapsulation is achieved by techniques known in the art. If hard capsules are used, this may be prepared of gelatin or HPMC.

In a further embodiment, the composition according to the invention may be packaged into a solid dosage form, e.g. by absorption to absorbing carriers, such as Neusilin® or Fujicalin®. The received dry granules can further be processed, e.g. by compression to tablets. The final solid formulation still maintains its property to be readily converted to a microemulsion *in vivo*, which thereby enhances the dissolution of the drug.

The invention is explained further by means of the following examples.

Examples

After preparation the SMEDDS were characterized with respect to their emulsification properties. Therefore, 0.1ml of the API-containing SMEDDS-solution is dissolved in 20ml of water for injection and sonicated for 5 min. The thereby formed specimen were visually assessed for their appearance and measured via photon correlation spectroscopy (PCS) for droplet size and polydispersity index (PDI).

Example 1

Tween® 80 (83.3 %) and soybean oil (16.7%) are mixed until a homogeneous liquid is obtained. Therein the active ingredient is dissolved under stirring at a concentration of 2.89 mg/ml. The emulsification property in aqueous media is summarized in table 1.

Example 2

Analogous to example 1 but the mixture is formulated as granulate by adding the SMEDDS to an absorbant.

Example 3

- 5 Analogous to example 2 but the mixture is packed into sachets.

Example 4

Analogous to example 2 but the mixture is packed into sticks.

Example 5

Analogous to example 2 but the mixture is processed into immediate-release tablets.

- 10 Example 6

Analogous to example 2 but the mixture is processed into orally-dispersible tablets.

Example 7

Analogous to example 2 but the mixture is processed into chewable tablets.

Example 8

- 15 Cremophor® ELP (75%) and Capmul® MCM (25%) are mixed until a homogeneous liquid is obtained. Therein the active ingredient is dissolved under stirring at a concentration of 2.4mg/ml. The emulsification property in aqueous media is summarized in table 1.

Example 9

- Labrafil M1944CS (30%) and Labrasol (70%) are mixed until a homogeneous liquid is obtained.
20 Therein the active ingredient is dissolved under stirring at a concentration of 2.9mg/ml. The emulsification property in aqueous media is summarized in table 1.

Example 10

- Propylene glycol (10%), ethanol (14%), Maisine 35-1 (36%) and Cremophor® RH40 (40%) are mixed until a homogeneous liquid is obtained. Therein the active ingredient is dissolved under stirring at a concentration of 2.33mg/ml.
25 The emulsification property in aqueous media is summarized in table 1 using the compound of formula (II) as active ingredient.

Table 1: Overview of visual assessment and PCS-results

Ex.	SMEDDS formulation	API conc. [mg/ml]	Appearance	largest peak (nm)	Z-Average	PDI (<0.5)
1	TWEEN 80 / soybean oil (83.3/16.7) (v/v)	2.89	clear	14.3	13.39	0.053
8	Cremophor ELP / Capmul MCM (75/25) (v/v)	2.4	clear	17.2	16.81	0.223
9	Labrafil M1944CS / Labrasol (30/70) (v/v)	2.9	turbid	287.1	248.5	0.177

Ex.	SMEDDS formulation	API conc. [mg/ml]	Appearance	largest peak (nm)	Z-Average	PDI (<0.5)
10	Propylenglycol / Ethanol / Maisine 35-1 / Cremophor RH40 (10/14/36/40) (v/v/v/v)	2.33	opalescent	97.8	64.56	0.408

Example 11

The in-vivo plasma pharmacokinetics of the compound of formula (II) were investigated in fasted male Wistar rats after single peroral administration of four SMEDDS (selected from above exam-
 5 ples based on the following main formulation component: Labrafil, Cremophor RH40, Cremophor ELP and Tween80) compared to a solution of a prodrug of the compound of formula (II).

The four SMEDDS were ready-to-use formulations for directly dosing of the animals with an ad-
 ministration volume of 5 mL/kg. Since the compound of formula (II) has a very low solubility in wa-
 ter for the purpose of comparison with the formulations according to the invention the hydrochlo-
 10 ride salt of the prodrug (i.e. 2-{4-[2-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-
 dicyano-6-(pyrrolidin-1-yl)pyridin-4-yl]phenoxy}ethyl L-alanyl-L-alaninate hydrochloride) is used to
 obtain a solution. This prodrug of the compound of formula (II) was dissolved in a PEG-400/EtOH-
 based formulation and dosed in 5 mL/kg to the animals.

The administered doses are related to the compound of formula (II). Plasma samples were col-
 15 lected at predefined time points up to 30 h post dosing for the SMEDDS and up to 96 h post dos-
 ing for the solution. The calculated pharmacokinetic parameters refer to the compound of formula
 (II) (analyte) and are summarized in the table below.

Example		2.41	9	10	8	1
Dose	[mg/kg]		14.5	11.65	12.0	14.45
Formulation		10% EtOH 40% PEG400 50% demin. water	30% Labrafil M1944CS, 70% Labrasol	40% Cremo- phor RH40, 36% Maisine, 14% Ethanol, 10% Propyl- ene glycol	75% Cremo- phor ELP, 25% Campul MCM	83.3% Tween80, 16.7% Sojaöl
Appl. Vol.	[mL/kg]	5	5	5	5	5
Animals		3	4	4	4	4
per time point						
AUC	µg • h/L	1910	16900	6800	6650	8670
AUC _{norm}	kg • h/L	0.794	1.17	0.584	0.554	0.600
t _{last}	h	96.0	30.0	30.0	30.0	30.0
C _{max}	µg/L	172	741	604	401	480
C _{max, norm}	kg/L	0.0716	0.0511	0.0519	0.0334	0.0333
t _{max}	h	3.00	5.00	5.00	5.00	7.00
t _{1/2}	h	22.9	16.4	5.98	10.3	8.95
R _{Points}		3	3-4	3-3	3-3	3-3
R _{Range}	h	32.0-96.0	5.00-30.0	7.00-30.0	7.00-30.0	7.00-30.0
t _{1/2} apparent	h	5.94				
R _{Points}		5				
R _{Range}	h	5.00-32.0				
F _{rel}	%	100	147	73.5	69.8	75.6

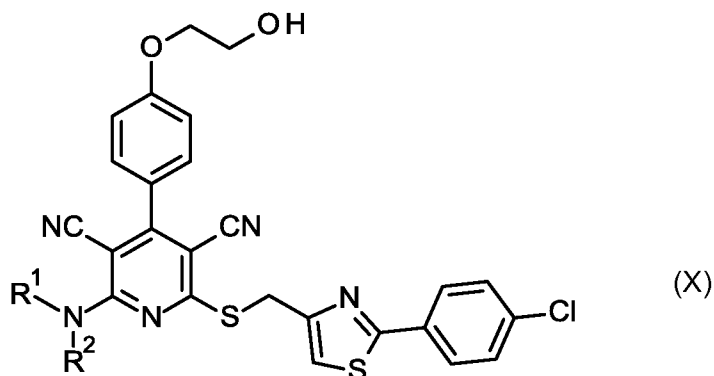
The exposure of the compound of formula (II) in terms of AUC_{norm} was $0.794 \text{ kg} \cdot \text{h/L}$ when administered as prodrug in solution. The exposures of the four SMEDDS were as follows: $1.17 \text{ kg} \cdot \text{h/L}$ for Labrafil, $0.584 \text{ kg} \cdot \text{h/L}$ for Cremophor RH40, $0.554 \text{ kg} \cdot \text{h/L}$ for Cremophor ELP and $0.60 \text{ kg} \cdot \text{h/L}$ for Tween80. The relative bioavailability (F_{rel} , prodrug solution set to 100 %) was 147% for Labrafil, thus
5 clearly higher than solution, and ranged between 70 % - 76 % for Cremophor RH40, Cremophor ELP and Tween80. Since the compound of formula (II) has a very low solubility in water it is thus surprising that such a high relative bioavailability can be reached using the SMEDDS formulations according to the invention, in one case even much higher when compared with the prodrug solution.

The maximum concentration of the compound of formula (II) in rat plasma was reached 3 h after
10 administration of the prodrug in solution, whereas t_{max} of the four SMEDDS was between 5 h – 7 h, thus somewhat later. The dose-normalized C_{max} of the compound of formula (II) was 0.0716 kg/L after dosing as prodrug in solution. C_{max} of the four SMEDDS was lower compared to solution ranging between 0.033 kg/L and 0.052 kg/L . The elimination half-life of the compound of
15 formula (II) was about 6 h determined in the interval up to 32 h when administered as prodrug in solution. The elimination half-life of the compound of formula (II) was slightly longer in Labrafil with approx. 16 h (interval up to 30 h), 10 h in Cremophor ELP (interval up to 30 h) and 9 h in Tween80 (interval up to 30 h) and was similar to solution with approx. 6 h in Cremophor RH40 (interval up to 30 h). Additionally, a long terminal elimination half-life of the compound of formula (II) was calculated for solution with about 23 h in the interval up to 96 h. However, no plasma sam-
20 ples were collected later 30 h post dosing after SMEDDS administration.

Claims

1. Composition comprising

- (a) a selective partial adenosine A1 receptor agonist of the formula (X)



in which

R¹ represents (C₁-C₄)-alkyl,

R² represents (C₁-C₄)-alkyl,

where (C₁-C₄)-alkyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of fluorine, trifluoromethyl, trifluoromethoxy, (C₁-C₄)-alkoxy, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkoxy and (C₁-C₄)-alkylsulphonyl,

or

R¹ and R² each represent hydrogen

or

R¹ and R² together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycle which may contain a further heteroatom from the group consisting of N, O and S,

where the 4- to 7-membered heterocycle may be substituted by 1 to 2 substituents independently of one another selected from the group consisting of fluorine, trifluoromethyl, (C₁-C₄)-alkyl, trifluoromethyl and (C₁-C₄)-alkoxy,

and the salts, solvates, and solvates of the salts thereof,

(b) an oil or lipid,

(c) a surfactant, and

(d) optionally a co-solvent or co-surfactant, or both.

2. The composition as claimed in claim 1, comprising a selective partial adenosine A1 agonist of the formula (X), in which

R¹ represents (C₁-C₃)-alkyl,

R² represents (C₁-C₃)-alkyl,

where (C₁-C₃)-alkyl may be substituted by 1 or 2 substituents independently of one another selected from the group consisting of fluorine, trifluoromethyl, methoxy, ethoxy, cyclopropyl and cyclobutyl,

or

R¹ and R² each represent hydrogen

or

R¹ and R² together with the nitrogen atom to which they are attached form a 4- to 6-membered heterocycle which may contain a further heteroatom from the group consisting of N, O and S,

where the 4- to 6-membered heterocycle may be substituted by 1 or 2 substituents independently of one another selected from the group consisting of fluorine, trifluoromethoxyl, (C₁-C₄)-alkyl, trifluoromethoxy, methoxy and ethoxy,

and the salts, solvates, and solvates of the salts thereof.

3. The composition as claimed in claims 1 or 2, comprising a selective partial adenosine A1 agonist of the formula (X), in which

R¹ represents ethyl,

R² represents ethyl,

or

R¹ and R² each represent hydrogen

or

R¹ and R² together with the nitrogen atom to which they are attached form an azetidiny, pyrrolidiny or piperidiny ring,

where the azetidiny ring may be substituted by a methoxy substituent,

and the salts, solvates, and solvates of the salts thereof.

4. The composition as claimed in any of claims 1 to 3, wherein the selective partial adenosine A1 agonist is selected from Capadenoson of formula (I) or Neladenoson of formula (II).

5. The composition as claimed in any of claims 1 to 4, wherein the oil or lipid is selected from the group consisting of medium- or long-chain glycerides, which contain fatty acids of varying chain lengths and degrees of unsaturation, of example Caprol 3GO (i.e. C8:C10 triglyceride), Labrafac® Lipophile WL 1349 {medium chain triglycerides [caprylic (C8) 50-80%, capric (C10) 20-50%]}, Labrafac® PG (propylene glycol dicaprylocarate), Labrafil® M 1944 CS {oleoyl polyoxyl-6 glycerides [oleic (C18:1) 58-68%, linoleic (C18:2) 22-32%]}, Labrafil® M 2125 CS {linoleoyl polyoxyl-6 glycerides [oleic (C18:1) 24-34%, linoleic (C18:2) 53-63%]}, Labrafil® M 2130 CS {lauroyl polyoxyl-6 glycerides}, Labrafac® CM 10 {C8-C10 polyglycolized glycerides [caprylic (C8) 50%, capric (C10) 50%]}, Labrafil® WL 2609 BS {linoleoyl macrogol glycerides [oleic (C18:1) 24-34%, linoleic (C18:2) 53-63%]}, Lauroglycol™ 90 {propylene glycol mono-

laurate Type II [monoesters > 90%, C12 (lauric acid) > 95%]], Lauroglycol™ FCC {propylene glycol laurate Type I [monoesters 45-70%, 30-55% diester >95% C12], Maisine™ 35-1 {glyceryl monolinoleate [C18:2 >50% max; C18:1 10-35%; C18:0 <6%; C16 4-20%]], Capryol™ 90 {propylene glycol monocaprylate [>90% monoester of C8 (caprylic acid)]}, Capryol™ PGMC 90 (propylene glycol monocaprylate; >60% Monoester >90% C8), Peceol™ {glyceryl mono-
 5 oleate [C18:1 > 60%; C18:2 < 35%; C18:0 < 6%; C16 < 12% 0-5%]], Plurol oleique® CC497 (polyglyceryl-3 dioleate), Plurol® (diisostearate triglycerol diisostearate), Transcutol® HP [diethylene glycol monoethyl ether (>99.9%)], Transcutol® P (diethylene glycol monoethyl ether), Captex® 355 (caprylic/capric triglyceride), Captex® 200 (propylene glycol dicaprylate/dicaprate), Migliol® 810 {medium chain fatty acids [C8 (65-80%); C10 (20-35%)]},
 10 Migliol® 812 {medium chain fatty acids [C8 (50-65%); C10 (30-45%)]}, Migliol® 840 (medium chain diesters of propylene glycols), Miglyol® 818 {medium chain fatty acids [C8 (45-65%); C10 (30-45%); C18:2 (2-5%)]}, Capmul® MCM {glyceryl monocaprylate [(58% monoglyceride, 36% diglyceride, 5% triglyceride; 80% C8, 20% C10)]}, Capmul® MCM C8 {glyceryl monocaprylate [(68% monoglyceride, 27% diglyceride, 3% triglyceride; >95% C8, 3% C10)]},
 15 Capmul® MCM C10 {glyceryl monocaprylate [(>45% monoglyceride; >45% C10)]}, Imwitor® 742 [monoglyceride/diglyceride/triglyceride of C8 and C10 fatty acid (45-55% monoglyceride)], Imwitor® 928 [monoglyceride/diglyceride/triglyceride of saturated fatty acids of coconut oil (40% MG)], Myrj® 45 {PEG 400 monostearate polyoxy 8 stearate [Stearic (C18) acid]}];

or natural product oils from apricot kernel, canola, castor, coconut, corn, olive, palm, palm kernel, peanut, safflower, sesame, soybean, sunflower.

6. The composition of claim 5, wherein the lipid is selected from Labrafil® M 1944 CS, Maisine™ 35-1, Capmul® MCM and soybean oil.

7. The composition as claimed in any of claims 1 to 6, wherein the surfactant has a hydrophilic-lipophilic balance (HLB) value of 12 or higher, for example Labrasol® {caprylocaproyl macro-
 25 gol-8-glycerides [caprylic (C8) 50-80%, capric (C10) 20-50%]}, Cremophor® EL or ELP (polyoxy-35-castor oil), Cremophor® RH40 (polyoxy-40-hydrogenated castor oil), Cremophor® A25 {Macrogol 25 cetostearyl ether [stearic (C18) and cetyl (C16)]}, Vitamin E® TPGS (Vit E d- α -tocopheryl polyethylene glycol 1000 succinate), Gelucire® 44/14 {lauroyl polyoxylglycerides [C12 (40-50%); C14 (14-24%); C8 (4-10%), C10 (3-9%), C16 (4-14%), C18 (5-5%)]}, Ge-
 30 lucire® 50/13 {stearoyl polyoxyl-32 glycerides [C16 (40-50%); C18 (48-58%); C16+18 > 90%]}, Acconon® CC-6 (PEG-6 caprylic/capric glycerides), Brij® 97 {polyoxyl 10 oleyl ether Oleth 10 PEG monooleyl ether [Oleyl (C18:1)]}, or Tween® 80 (polysorbate 80).

8. The composition of claim 7, wherein the surfactant is selected from Labrasol®, Cremophore® RH40, Cremophore® EL, Cremophor® ELP and Tween® 80.

9. The composition as claimed in any of claims 1 to 8 comprising

(a) a selective partial adenosine A1 receptor agonist,

(b) 10 to 50 % (v/v) of an oil or lipid,

(c) 35 to 85 % (v/v) of a surfactant, and

5 (d) 0 to 40 % (v/v) of a co-solvent or co-surfactant, or both.

10. A process for preparing the compositions according to claims 1 to 9, characterized in that excipients (b) and (c) and optionally (d) are mixed until a clear solution is obtained, and that in a second step the selective partial adenosine A1 receptor agonist is dissolved in this mixture under stirring.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/063778

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K9/107 A61K47/10 A61K47/14 A61K47/26 A61K47/44 A61K31/4439 ADD. According to International Patent Classification (IPC) or to both national classification and IPC																	
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, BIOSIS, WPI Data																	
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>Y</td> <td>DE 10 2009 006602 A1 (BAYER SCHERING PHARMA AG [DE]) 5 August 2010 (2010-08-05) paragraphs [0077], [0078], [0280] - [0281] -----</td> <td>1-10</td> </tr> <tr> <td>Y</td> <td>WO 2008/147939 A1 (KING PHARMACEUTICALS RES & DEV [US]; BEASLEY MARTIN W [US]; HAUSE DAVI) 4 December 2008 (2008-12-04) examples -----</td> <td>1-10</td> </tr> <tr> <td>A</td> <td>WO 2006/057903 A2 (MERCK & CO INC [US]; PERESYPKIN ANDREY V [US]; DOKOU ELENI [US]; MCKEL) 1 June 2006 (2006-06-01) examples -----</td> <td>1-10</td> </tr> <tr> <td>A</td> <td>WO 2009/024590 A2 (BASILEA PHARMACEUTICA AG [CH]; BUCHER CHRISTIAN [CH]; DITZINGER GUENTE) 26 February 2009 (2009-02-26) examples -----</td> <td>1-10</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	Y	DE 10 2009 006602 A1 (BAYER SCHERING PHARMA AG [DE]) 5 August 2010 (2010-08-05) paragraphs [0077], [0078], [0280] - [0281] -----	1-10	Y	WO 2008/147939 A1 (KING PHARMACEUTICALS RES & DEV [US]; BEASLEY MARTIN W [US]; HAUSE DAVI) 4 December 2008 (2008-12-04) examples -----	1-10	A	WO 2006/057903 A2 (MERCK & CO INC [US]; PERESYPKIN ANDREY V [US]; DOKOU ELENI [US]; MCKEL) 1 June 2006 (2006-06-01) examples -----	1-10	A	WO 2009/024590 A2 (BASILEA PHARMACEUTICA AG [CH]; BUCHER CHRISTIAN [CH]; DITZINGER GUENTE) 26 February 2009 (2009-02-26) examples -----	1-10
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Date of the actual completion of the international search 24 July 2018		Date of mailing of the international search report 02/08/2018															
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Giménez Miralles, J															

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